



## **CBD as a potential treatment for intractable epilepsy**



**by Orrin Devinsky, MD**

Marijuana (*Cannabis sativa* and *indica*) is a naturally growing plant with many chemical constituents present in varying levels in the different varieties. More than 80 cannabinoids and 400 non-cannabinoid constituents have been identified. The main constituents of marijuana are delta-9-tetrahydrocannabinol (D<sup>9</sup>-THC), the main psychoactive constituent, and cannabidiol (CBD) the main non-psychoactive constituent. Unlike D<sup>9</sup>-THC which binds to the cannabinoid receptors 1 and 2 to exert its psychoactive effects, CBD has little affinity for either cannabinoid receptor. However, while CBD is known to affect multiple biological mechanisms in cell-based tests, it is not yet known which, if any, are responsible for its anticonvulsant actions in animal models of epilepsy. Dr. Ben Whalley at the University of Reading, UK, continues to work to uncover CBD's anticonvulsant mechanism of action. He has a particular focus on establishing the relevance of CBD's anti-inflammatory and neuroprotective properties in rodent models that best model adult and pediatric treatment resistant epilepsies.

In the 19th century, marijuana was used to treat epilepsy by Drs William Gowers and Russell Reynolds, two of the English founders of modern epilepsy. A Cochrane report from 2012 compiled studies on cannabinoids for epilepsy. This report included 4 clinical studies where CBD was used to treat various adults with treatment-resistant epilepsy. Beneficial effects on seizure control were reported in many of these patients, but the studies included few subjects and the methods were limited. More recently, with the introduction of legalized medicinal marijuana products in Colorado

and California, parents of children with Dravet Syndrome and other treatment resistant epilepsies have given products with high CBD:THC ratios (e.g., in the range of 15:1 to 24:1). Many parents have reported benefits for seizure control, behavior, and cognition; although the results vary and some parents have only reported improved seizure control while others reported only improvement in cognition. Side effects were infrequently reported, with tiredness as the main one. These observations, together with positive results from several different animal models, have shown that CBD can prevent or reduce the intensity of seizures and suggest that additional studies of CBD in Dravet Syndrome and other treatment-resistant epilepsies are needed. However, other studies have found that THC can cause significant short-term behavioral changes and long-term cognitive changes in children. This suggests that use of medical marijuana preparations containing THC should be used cautiously until more safety data is available (Andreasson, 1987; Caspi 2005; DiForti 2012).

The NYU Epilepsy Centers have recently obtained FDA approval to treat 25 children and young adults, ages 1-30, with Dravet Syndrome, Lennox Gastaut Syndrome, and other treatment resistant epilepsies. The CBD to be used is supplied by [GW Pharmaceuticals](#) through their investigational pure CBD compound, Epidiolex™ which is derived from cannabis plants. The study duration is 64 weeks. Similar studies will hopefully soon be underway at other medical centers around the country (UCSF, MGH, Northwestern Children's, and Children's Hospital of Philadelphia). These observational studies will assess how different doses of CBD are tolerated, look carefully at safety measures and examine the potential for drug interactions. Specific inclusion and exclusion criteria for these observational studies may vary between sites. While seizure frequency will also be evaluated, the tolerability, not effectiveness, of CBD will be the main goal of these initial studies. We hope to move forward in the near future with a separate multicenter, randomized controlled trial of CBD for treatment-resistant Dravet and Lennox Gastaut Syndromes to assess CBD's effectiveness.

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### **Obtaining Epidiolex™ in the U.S.**

DSF would like to provide instructions on obtaining Epidiolex™ in the United States for those who are interested. The process for obtaining Epidiolex™ is very different from that which many families previously used with stiripentol. Epidiolex™ can only be obtained through an expanded access Investigational New Drug (IND) application, which the patient's physician submits to FDA.

It starts with the patient's physician needing to write directly to GW's in-house physician, Dr. Eltayb ([info@gwpharm.com](mailto:info@gwpharm.com)), explaining that he/she is interested in obtaining GW's pure investigational CBD compound, Epidiolex™, to treat one or more patients with intractable epilepsy. Dr. Eltayb will then connect with the physician and send the physician a formal response, with a request form to be filled out. If the request is approved by GW, subject to certain conditions GW will agree to provide the CBD to that physician, and will send the physician detailed information about the product. The physician then files the IND, and if the FDA approves it, the physician's hospital Institutional Review Board (IRB) allows it, and the Drug Enforcement Administration licenses the site, GW will send the product directly to the physician, who will administer it according to the treatment plan laid out in the IND. GW can provide some helpful information to the physician about the FDA and DEA procedures.

With regard to cost, GW will need to make a charge for Epidiolex. However, GW has informed DSF that no patient will have to pay for Epidiolex™ unless the patient's physician has determined that the patient is significantly benefiting from the treatment. Consequently, patients will be given a three (3) month free-of-charge period for their physicians to ascertain whether Epidiolex™ is helping them. After that period, the FDA will determine what costs GW can pass along to patients. The FDA does not allow a company to make a profit from products that are not FDA-approved. The exact amount of the charge therefore cannot exceed GW's manufacturing, testing, and shipping costs. A patient's actual daily dose will determine that patient's monthly/annual cost.